

## **REMARKS**

### **I. Status of the claims and support for the amendment.**

Claims 16 and 21 are cancelled herein

Claims 1, 14, and 18 are amended.

Claims 1, 2, 4–15, 17–20, and 22 are currently pending.

Support for the amendment of the claims is found in claims 8, 16, and 21 as originally filed. Applicant explicitly reserves the right to pursue any cancelled material in one or more divisional applications.

### **II. Rejection under 35 U.S.C. §103**

A. Claims 1, 2, and 4–22 are rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Magruder (USP 5,037,420) and Mitchell (USP 5,474,980). Specifically, the Examiner alleges that Magruder and Mitchell:

teach the elements of the claimed invention...It would have been obvious to one of ordinary skill in the art at the time the invention was made to have formulated the composition disclosed by Magruder in the biocompatible oil/aluminum stearate vehicles taught by Mitchell because Mitchell teaches that the oil/monostearate vehicles are useful for prolonged parenteral release of somatotropin *in vivo*.

As noted in the prior response MPEP chapter 2100 sets forth the standard which must be satisfied in combining two references. It states, in pertinent part:

“[t]here are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art.” *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obviousness was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

*MPEP §2143.01*. MPEP 2143.01 further states that “[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).” Emphasis in the original.

It is Applicant’s understanding that the Examiner’s position is that the combination of the cited art teaches “elements” that when combined provide the instant invention. Applicant respectfully traverses.

In an effort to clarify Applicant’s understanding of the rejection, Applicant offers the following analysis, by way of example only. This example is not to be construed as a concession or a limitation on the instantly claimed invention. It is Applicant’s understanding that rejection alleges that one of ordinary skill in the art, upon examining the contents of Magruder and Mitchell would be motivated to provide the instantly claimed invention. Thus, the rejection apparently asserts that all the elements of the instantly claimed invention are taught in the prior art and that the prior art provides the motivation to combine those elements to provide the instantly claimed invention.

Moreover, the rejection indicates that Mitchell teaches that “oil/monosterate vehicles are useful for prolonged parental release of somatotropin *in vivo*.” In order for the rejection to be proper, one must look to the combination of the cited art to provide all of the claim elements and the motivation to combine them. That is all “elements” of the instantly claimed invention must be taught by the combination of Magruder with Mitchell and there must be motivation to combine Mitchell’s “vehicles” with “elements” taught by Magruder in such a way as to provide the instant invention.

Page 2 of the office action, asserts, *inter alia*, that the claimed invention is drawn to a composition of matter comprising: human, equine, bovine or porcine somatotropin (ST). Applicant firstly wishes to clarify that not all claims are limited to the specifically recited types of somatotropins. Only those claims wherein the specific types of somatotropin are recited are so limited.

The current claims are drawn to compositions comprising: (1) somatotropin; (2) a first bioavailability enhancing constituent (BEC) comprising a non-ionic surfactant; and (3) optionally a second BEC comprising a “non-reducing carbohydrate” and/or an “oxo-acid salts.” The claims further require that the BEC(s) and ST must be suspended in a “substantially non-aqueous hydrophobic carrier.”

In order to render the current claims obvious the instant rejection would have to accurately assert that the combination of Magruder and Mitchell teach or suggest the combination of ST and a “non-ionic surfactant” “suspended in a substantially non-aqueous carrier”.

It is Applicant’s contention that the combination of Magruder and Mitchell cannot be properly be argued as either teaching or suggesting such a composition. Although Magruder does suggest compositions comprising surfactants, the reference teaches that acceptable surfactants comprise “anionic, cationic, amphoteric and nonionic surfactants” (Col. 15, lines 42 and 43). There is no teaching that non-ionic surfactants are preferable. Furthermore, Magruder indicates that the surfactants are used as part of an aqueous solution (*see*, column 16, lines 4–8, which recites in pertinent part that “[g]enerally, the compartment 18 composition comprises from 0.5% to 50% beneficial agent, [and] *from 20% to 45% aqueous buffer...and from 0.001% to 7.5% surfactant*” (emphasis added)) or as a “*buffer-aqueous-solution*” (*see* col. 15, lines 34 and

35, emphasis added) . Magruder provides no teaching or suggestion that it would be desirable or advantages to provide a composition where bST and surfactant are suspended in a “substantially, non-aqueous hydrophobic carrier.

*MPEP §2143.01* states, *inter alia*, that “[i]f [a] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).” Applicant, asserts that modification of the use of the surfactant to suspend it in a “substantially non-aqueous hydrophobic carrier” as proposed by the instant rejection renders the surfactant unsuitable for use in conjunction with an “aqueous buffer” solution as taught in Magruder *et al.* Accordingly, there is no teaching or motivation to make the proposed modification.

Finally, as the sub-heading of MPEP §716 states “Greater than expected results are evidence of non-obviousness”. The section further recites, *inter alia*, that:

“[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue.” *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985)...Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. “Evidence that a compound is unexpectedly superior in one of a spectrum of common properties...can be enough to rebut a *prima facie* case of obviousness.” No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow sedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. §103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.).

*See, MPEP §716.02(a)*

As stated in the Specification (*see, e.g.* page 9, lines 4–14) and demonstrated by the data presented in the Figures (*see* figures 1-6), the compositions of the instant invention provide unexpectedly superior results when compared the closest cited art. Figures 1–4 show that compositions comprising a non-ionic surfactant as the first bioavailability-enhancing constituent (BEC) exhibit dramatically improved serum bST concentration in rodents and calves. Figures and 6 show improved weight gain in female rodents treated with compositions of the instant invention.

Additionally, there is nothing in the combination of Magruder and Mitchell that teaches or suggests that a composition comprising a non-ionic surfactant and a somatotropin suspended in a substantially non-aqueous hydrophobic carrier would provide the enhanced bioavailability characteristics exhibited by the instantly claimed invention. Assuming, *arguendo*, that Mitchell teaches that oil/monostearate vehicles are useful for prolonged release of somatotropin *in vivo*, this would not lead the artisan of ordinary skill to conclude that the currently claimed compositions would have increased and prolonged bioavailability with respect to bST compositions comprising oil/monostearate (*e.g.* POSILAC®).

In view of the standard set out in *MPEP 716.02(a)*, Applicant asserts that the unexpectedly advantageous properties of the instantly claimed invention, as demonstrated by the clearly superior results summarized in figures 1–6 and described in Examples 1–7, provide unequivocal evidence sufficient to demonstrate the non-obviousness of the instantly claimed invention. Accordingly, Applicant believes that the rejection of the claims as being obvious in view of Mitchell and Magruder has been overcome and may now properly be withdrawn.

**B.** The §103 rejection further alleges that claim 2 is over the combination of Magruder and Mitchell in further view of Scarborough (U.S. Pat. No. 6,162,258). The rejection recites that:

Scarborough teaches a polyoxyethylene sorbitan fatty acid ester and a polyoxyethylene fatty acid ester mixed with a growth hormone such as a somatotropin[].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have added the non-ionic surfactants of Scarborough to the composition disclosed by Magruder in view of Mitchell in order to enhance the bioavailability of somatotropin in the composition, because Scarborough teaches biocompatibility in the healing process.

Applicant respectfully traverses.

Even if, as alleged, Scarborough teaches the compositions of the listed non-ionic surfactants and somatotropins (an allegation that Applicant does not concede), the addition of the Scarborough reference does nothing to render claim 2 obvious. For the reasons set out in part “A.”, above, Applicant contends that there is no motivation to combine Magruder and Mitchell. Moreover, the criteria set out in *MPEP* §716.02(a) provide that the unexpectedly superior results demonstrated for instantly claimed invention, (*see* Figures 1–6 and Examples 1–7) are sufficient to rebut a *prima facie* case of obviousness).

Furthermore, as noted in a prior response, Scarborough does not teach mixtures of somatotropins and surfactants. Instead it teaches only the use of certain surfactants as a few of scores of possible “strength conserving agents” to help preserve the strength of monolithic bone during lyophilization (*see* columns 4 and 5). Said monolithic bone must then be rehydrated prior to use. Growth hormones are listed as one of many possible agents that are useful as part of the “rehydration solution.” Accordingly, the only composition comprising a combination of a surfactant and a growth hormone taught by Scarborough would be where the bone is rehydrated in an aqueous solution comprising growth hormone. Thus, there is nothing in Scarborough, when taken in combination with Magruder and Mitchell, that teaches or suggest a substantially non-aqueous composition comprising a somatotropin and a surfactant. Moreover, the fact that

Scarborough teaches that the composition is biocompatible, would not suggest to one of ordinary skill in the art that the composition would have enhanced bioavailability. Enhanced bioavailability is only shown by the examples provided in the current Specification.

Thus, it is Applicant's position that the addition of the Scarborough patent to the cited art does nothing to change the conclusion reached in part "A." of this response to the obviousness rejection. That is, Scarborough adds nothing, when taken in combination with Magruder and Mitchell that would motivate one of ordinary skill in the art to modify the compositions taught in these references so as to provide the instantly claimed invention of claim 1. Given that claim 2 depends from and further limits claim 1, there is, likewise, nothing in the combination of the cited art that renders claim 2 obvious.

In view of the foregoing, Applicant believes that the rejection of claim 2, as being obvious over the combination of Magruder, Mitchell, and Scarborough, has been overcome and may now properly be withdrawn.

In view of the foregoing arguments, Applicant believes that the rejection of claims 4 and 5, as allegedly being obvious over the combination of Magruder, Mitchell, and Hamilton, has been overcome and may now properly be withdrawn.

C. Finally, claims 6 and 7 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Magruder and Mitchell in further view of Hamilton (U.S. Pat. No. 4,816,568). The rejection recites that:

Hamilton teaches a stabilized growth hormone formulation that can be compressed into a tablet or pellet form. When combined with the teachings of Magruder and Mitchell it would have been obvious to one of ordinary skill in the art at the time the invention was made to have added the polyol stabilizer of Hamilton to the composition disclosed by Magruder in view of Mitchell in order to enhance the bioavailability of the somatotropin in the composition, because

Hamilton teaches that growth hormones can be admixed with various stabilizers to provide for the preservation of the soluble bioactivity of the growth hormone.

Applicant respectfully traverses.

Even if, as alleged, Hamilton teaches the admixture of somatotropins with polyols to preserve soluble activity (an allegation that Applicant does not concede), the addition of Hamilton does nothing to render the instantly pending claims 6 and 7 obvious. For the reasons set out in part "A.", above, Applicant contends that there is no motivation to combine Magruder and Mitchell. Moreover, the criteria set out in *MPEP* §716.02(a) provide that the unexpectedly superior results demonstrated for instantly claimed invention, (*see* Figures 1–6 and Examples 1–7) are sufficient to rebut a *prima facie* case of obviousness).

It is Applicant's position that the additional citation of the Hamilton patent does nothing to change the conclusion reached in part "A." of this response to the obviousness rejection. That is, Hamilton adds nothing, when taken in combination with Magruder and Mitchell that would motivate one of ordinary skill in the art to modify the compositions taught in these references so as to provide the instantly claimed invention of claim 1. Given that claims 6 and 7 depend from (either directly or indirectly) and further limit claim 1, there is, likewise, nothing in the combination of the cited art that renders claims 6 and 7 obvious.

In view of the foregoing arguments, Applicant believes that the rejection of claims 6 and 7, as allegedly being obvious over the combination of Magruder, Mitchell, and Hamilton, has been overcome and may now properly be withdrawn.

### **III. Conclusion**

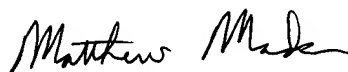
In view of the foregoing arguments and the discussion with the Examiner during the October 22, 2003 telephone interview, Applicant believes that all rejections of the currently



pending claims have been overcome and that the instant case is now in condition for immediate allowance. Accordingly, Applicant respectfully requests a favorable reconsideration of the instant case and issuance of a "Notice of Allowance" therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Matthew L. Madsen  
Reg. No. 45,594  
Patent Agent for Assignee  
MONSANTO TECHNOLOGY LLC

HOWREY SIMON ARNOLD & WHITE, LLP  
750 Bering Drive  
Houston, Texas 77057-2198  
(713) 787-1400

Date: October 22, 2003